

12

EUROPEAN PATENT APPLICATION

Application number: 85305303.1

Int. Cl.⁴: **C 07 J 5/00**
A 61 K 9/72

Date of filing: 25.07.85

Priority: 25.07.84 PT 78972
11.07.85 PT 80796

Date of publication of application:
26.02.86 Bulletin 86/9

Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

Applicant: HOVIONE INTER LTD.
P.O. Box 1500
CH-8305 Dietlikon Zurich(CH)

Inventor: Page, Philip Ronald Rua dos Girassols
Lote 38 A Bairro de Santo Antonio
Sao Domingos de Rana P-2775 Parada(PT)

Inventor: Haggie, William
Rua Elais Garcia No. 29-6 Esq
P-2830 Barreiro(PT)

Representative: Wain, Christopher Paul et al,
A.A. THORNTON & CO. Northumberland House 303-306
High Holborn
London WC1V 7LE(GB)

Preparation and use of new solvates of beclomethasone 17,21-dipropionate.

Novel di-isopropyl ether solvates of beclomethasone 17,21-dipropionate are prepared by dissolving beclomethasone 17,21-dipropionate in an organic solvent and precipitating the solvate by addition of di-isopropyl ether. The solvates are substantially bulk-stable and find utilisation, inter alia, in aerosol formulations.

PREPARATION AND USE OF NEW SOLVATES OF
BECLOMETHASONE 17,21-DIPROPIONATE

5 The present invention refers to the preparation of di-isopropyl ether solvates of beclomethasone 17,21-dipropionate. These new solvates are substantially bulk-stable, in both the non-micronised and the micronised forms. The micronised form is especially indicated for use in the preparation of stable aerosol formulations.

10 The use of beclomethasone 17,21-dipropionate per se in the treatment of asthmatic complaints has been known for some time, for example see Morrow Brown et al., British Medical Journal 1, 585-90 (1972). Since this time, the preparation of stable aerosols has been of significant importance. The use of halogenated hydrocarbons was first described in British Patent
15 1,429,184, and later in British Patent Application 2,076,422. However, the halogenated hydrocarbon solvates therein produced, including that of beclomethasone 17,21-dipropionate, were found not to be bulk stable. Since that time, other solvates have been claimed, such as hydrocarbon solvates in European Patent Specification 39,369, the ethyl acetate solvate in German
20 Offenlegungsschrift 3,018,550 and the monohydrate in British Patent Application 2,107,715.

It is taught in British Patent 1,429,184 that the suitable particle size of a steroid for inhalation into the bronchial system is between 2 and 5 microns. It is further taught that beclomethasone 17,21-dipropionate
25 crystals in aerosol formulations are prone to the phenomenon of crystal growth and/or crystal agglomeration, wherein crystals of particle size above 20 microns are formed. Such crystals can cause clogging of the metering valve in the aerosol, and are also too large to penetrate far enough into the bronchial system.

30 According to the present invention, there is provided a process for the preparation of new di-isopropyl ether solvates of beclomethasone 17,21-dipropionate, characterised by the fact that beclomethasone 17,21-dipropionate is dissolved in an organic solvent and is precipitated by addition of di-isopropyl ether. A further feature of the present invention are the
35 novel solvates produced by the above process.

We have now found that solvates of beclomethasone 17,21-dipropionate with di-isopropyl ether can be prepared, which are substantially bulk stable with respect to the solvate present. Further, these new solvates can be

micronised by conventional methods, such as by a fluid energy mill, and it has been surprisingly found that those micronised solvates are also substantially stable. Further, it has been unexpectedly established that such micronised solvates, when used in aerosol formulations, do not exhibit
5 any significant crystal growth or agglomeration.

The process of the present invention is conveniently carried out using a mixed solvent system, consisting of di-isopropyl ether and an organic solvent, which is both miscible with or soluble in di-isopropyl ether and in which the beclomethasone 17,21-dipropionate is soluble. The
10 preferred organic solvent can be chosen from the group comprising halogenated hydrocarbons such as chloroform and dichloromethane and ethers such as tetrahydrofuran and dioxan.

The beclomethasone 17,21-dipropionate is dissolved in the organic solvent, at between room temperature and the reflux temperature of the
15 organic solvent. Then sufficient di-isopropyl ether is added, with constant stirring, until complete crystallisation occurs. Alternatively, only sufficient organic solvent is used to just dissolve the beclomethasone 17,21-dipropionate, and then di-isopropyl ether is added until the mixture becomes slightly turbid. Upon cooling slowly to about 0°C, the solvate
20 crystallises out of the mixture.

The required crystalline solid can be obtained by conventional means, such as filtration, washing with di-isopropyl ether, followed by drying. The dried solid is then micronised by known techniques, such as by a fluid energy mill or by ball milling. The particle size range is preferably
25 between 2 and 5 microns, which can be obtained either directly from the micronisation technique or by sieving.

The solvates thus obtained have been analysed by various techniques. Thus, the infra-red spectra of beclomethasone 17,21-dipropionate and of a di-isopropyl ether solvate show a significant difference in the region of
30 3200 - 3500 cm^{-1} . This is due to the fact that in the solvated crystal, hydrogen bonding is eliminated because of the presence of the solvating molecules and this causes the broad band at 3280 cm^{-1} in the non-solvated crystal to move to 3500 cm^{-1} in the solvated crystal. Similarly, other differences are apparent, for example in the carbonyl stretching frequencies
35 at approximately 1720 cm^{-1} , and in other regions throughout the entire spectra.

In order to ascertain the exact quantity of solvate present, a loss on drying test at 105°C under vacuum can be conveniently used. It has been thus shown that the loss on drying is usually about 10% weight/weight.

5 An analysis by gas chromatography indicated that both the diisopropyl ether, and the organic solvent used in the crystallisation mixture, were incorporated into the crystal structure of the solvate.

10 Thus the beclomethasone 17,21-dipropionate is in reality solvated with a pair of solvating molecules. These solvating molecules are present in molar proportions ranging from 1 to 6 moles/mole of beclomethasone 17,21-dipropionate.

15 A further feature of the invention is a stable aerosol formulation containing the solvates prepared as above. The propellants and actual aerosol cannisters and valves to be used are well known to those skilled in the art. Preferably, the propellants comprise trichlorofluoromethane (Freon 11^R) and dichlorodifluoromethane (Freon 12^R).

20 Typically the aerosol will supply metered doses of 50 µg of the active principle. The usual maximum daily dose is about 600 µg of beclomethasone 17,21-dipropionate. The presence of about 10% weight/weight of di-isopropyl ether plus the organic solvent used in the crystallisation mixture is thus not considered to have any significant toxic effect.

25 The following examples will serve to illustrate the invention, without in any way limiting the scope thereof.

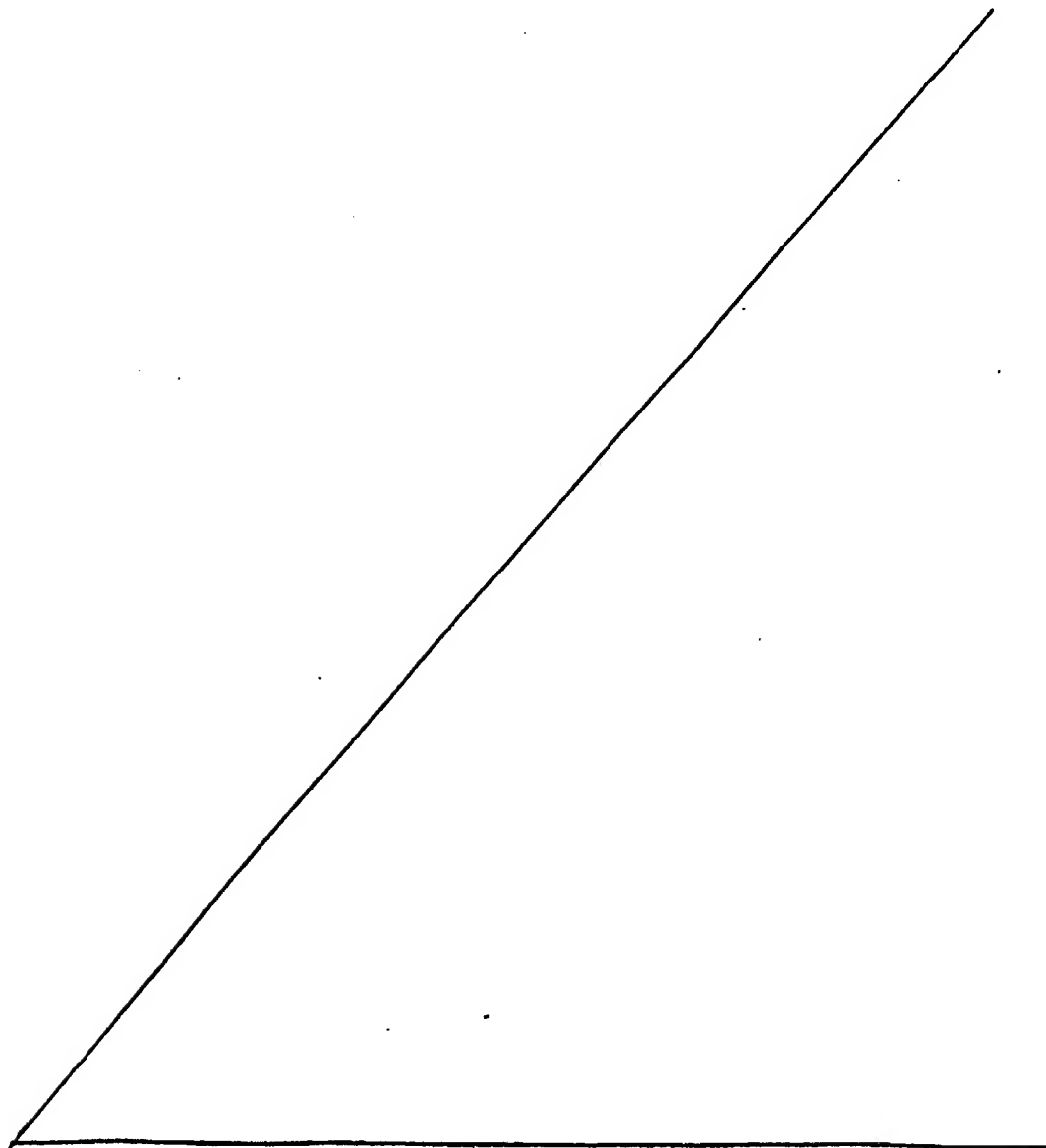
EXAMPLE 1 - Preparation of Beclomethasone 17,21-dipropionate di-isopropyl ether solvate

30 Method A:

Beclomethasone 17,21-dipropionate (100.0 g; 0.192 moles) was dissolved in chloroform (1 lt.) The solution was filtered and di-isopropyl ether (4 lts.) was added with constant stirring. The stirring was then continued for a further hour, the solid so formed was then filtered, washed with a small quantity of di-isopropyl ether and dried at 35°C. The yield of the solvate was 104.9 g.

The product had the following analysis:

- 5
- Loss on drying : 10.8% (dried under vacuum at 105°C to constant weight)
 - Gas chromatography : 6.9% (di-isopropyl ether)
3.0% (chloroform)
 - Karl Fischer : 0.4% (water)
 - Melting point : 210-2°C



Method B:

Beclomethasone 17,21-dipropionate (50.0 g; 0.096 moles) was dissolved in chloroform (500 ml) and the resulting solution filtered. Di-isopropyl ether saturated with water (2 lts.) was then added with constant stirring and the stirring then continued for a further hour. The precipitate was filtered, washed with di-isopropyl ether and dried at 35°C. The yield of beclomethasone 17,21-dipropionate di-isopropyl ether solvate was 47.7 g and had the following analysis:-

- Loss on drying : 12.7% (dried under vacuum at 105°C to constant weight)
- Gas chromatography : 6.9% (di-isopropyl ether)
4.5% (chloroform)
- Karl Fischer : 0.57% (water)
- Melting point : 211-2°C

Method C:

Dioxan (500 ml) was added to beclomethasone 17,21-dipropionate (100.0 g; 0.192 moles) and the mixture warmed to dissolve the solid material. The solution was then filtered and di-isopropyl ether (5 lts.) added with constant stirring. After complete precipitation, the mixture was cooled in an ice bath and the solid filtered, then washed with di-isopropyl ether and dried at 35°C. The yield of the dioxan/di-isopropyl ether solvate was 110.5 g. After micronisation, the product had the following analysis:-

- Loss on drying : 11.4% (dried under vacuum at 105°C to constant weight)
- Gas chromatography : 3.0% (di-isopropyl ether)
7.2% (dioxan)
- Karl Fischer : 0.91% (water)
- Melting point : 210-1°C

Method D:

Beclomethasone 17,21-dipropionate (100.0 g; 0.192 moles) was dissolved in tetrahydrofuran (500 ml) with slight warming and the resulting solution filtered. Di-isopropyl ether (5 lts.) was then added under constant stirring and the mixture cooled to 0°C. The solid was then filtered, washed with a small quantity of di-isopropyl ether and dried at 35°C. The yield of

solvate was 109.1 g. After micronisation, the beclomethasone 17,21-dipropionate tetrahydrofuran/di-isopropyl ether solvate had the following analytical values:-

- 5 - Loss on drying : 10.5% (dried under vacuum at 105°C to constant weight)
- Gas chromatography : 6.5% (di-isopropyl ether)
- 4.5% (tetrahydrofuran)
- Karl Fischer : 0.97% (water)
- Melting point : 210-1°C

10

EXAMPLE 2- Oral inhalation spray formulation

A spray formulation of di-isopropyl ether solvate of beclomethasone 17,21-dipropionate can be prepared as follows:-

15	Beclomethasone 17,21-dipropionate di-isopropyl ether solvate	10.0 mg
	Linoleic acid	10.0 mg
	Trichlorofluoromethane	9.99 g
	Dichlorodifluoromethane	15.00 g

20 The linoleic acid is efficiently mixed with cold trichlorofluoromethane, then the micronised beclomethasone 17,21-dipropionate di-isopropyl ether solvate is added. The mixing is continued until a completely uniform mixture is obtained, with any trichlorofluoromethane lost by evaporation, being replaced. Each inhaler is filled with the required amount after which

25 the valve is attached, and the required dichlorodifluoromethane pumped in.

CLAIMS

1. Process for the preparation of di-isopropyl ether solvates of beclomethasone 17,21-dipropionate, characterised by the fact that 5 beclomethasone 17,21-dipropionate is dissolved in an organic solvent and is precipitated by addition of di-isopropyl ether.
2. Process according to claim 1, characterised by the fact that the organic solvent is chosen from a group comprising halogenated hydrocarbons 10 and ethers.
3. Process according to claim 2, characterised by the fact that the halogenated hydrocarbon is chloroform or dichloromethane.
- 15 4. Process according to claim 2, characterised by the fact that the ether is tetrahydrofuran or dioxan.
5. Process according to claim 1, characterised by the fact that the solvate prepared by this process contains about 10% of solvating substances. 20
6. Process for the preparation of stable aerosols, characterised by the fact that propellant gases such as trichlorofluoromethane or dichlorodifluoromethane are used and the di-isopropyl ether solvate of beclomethasone 17,21-dipropionate is contained in aerosol inhalers/canisters. 25
7. Solvates of beclomethasone 17,21-dipropionate containing di-isopropyl ether, preferably between 3 and 10% by weight.



European Patent
Office

EUROPEAN SEARCH REPORT

0172672

Application number

EP 85 30 5303

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D, A	EP-A-0 039 369 (SCHERING CORP.) * Claims *	1-7	C 07 J 5/00 A 61 K 9/72
D, A	US-A-4 044 126 (P.B. COOK) * Claims 1, 2, 4-13 *	1-7	
D, A	GB-A-2 107 715 (GLAXO) * Claims *	1-7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 J 5/00 A 61 K 9/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 23-10-1985	Examiner HENRY J.C.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			